Journal: **Ageing Research Reviews (IF 10.3)**

Effects of transcranial electrical stimulation on episodic memory in physiological and pathological ageing

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Declaration of interest: none

Keywords
tES, tDCS, so-tDCS, episodic memory, interventions, long-term memory

Abstract

Memory for personally-relevant past events (episodic memory) is critical for activities of daily living. Decline in this type of declarative long-term memory is a common characteristic of healthy ageing, a process accelerated in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD).

Transcranial electrical stimulation (tES) has been used as a strategy to ameliorate episodic memory. Here, we critically review studies investigating whether tES may improve episodic memory in physiological and pathological ageing.

Most of the studies suggest that tES over the prefrontal or temporoparietal cortices can have a positive effect on episodic memory, but the transfer to improvement of execution of daily living activities is still unknown. Further work is needed to better understand the mechanisms underlying the effects of stimulation, combine tES with neuroimaging and optimizing the dosing of stimulation. Future studies should also investigate the optimal timing of stimulation and the combination with medications to induce long-lasting beneficial effects in pathological ageing.

More open science efforts should be done to improve rigor and reliability of tES in ageing research.

1. Introduction

Episodic memory refers to the memory for individual life events that contain detailed information on what has happened and where and when these events took place (Tulving, 1983). Neuropsychological works have demonstrated that this type of declarative long-term memory relies on the integrity of the medial temporal lobe (MTL), which includes the hippocampus and adjacent brain areas (perirhinal, parahippocampal, and entorhinal cortex) (Dickerson and Eichenbaum, 2010). Neuroimaging and lesion studies have also showed the contribution of prefrontal cortex (e.g. ventrolateral and dorsolateral) and temporoparietal cortex to episodic memory processes (Fletcher and Henson, 2001; Manenti et al., 2012b; Rugg and King, 2018; Spaniol et al., 2009; Szczepanski and Knight, 2014). In addition, accumulating evidence shows that functional interactions between these brain areas and the hippocampus are vital for episodic memory (Eichenbaum, 2017; Simons and Spiers, 2003; Wang et al., 2014).

From a cognitive perspective, memories are acquired, stored, maintained and retrieved. For a limited time after encoding memories are unstable (fragile) and vulnerable to interference, but as time passes, memories stabilize or consolidate and become resistant to interference (McGaugh, 2000). The first type of consolidation process is at cellular level. Morphological changes are important for memory stabilization in the hippocampal paths. This process takes place in the first few hours after encoding. The second type of consolidation is at the systems-level. It refers to the gradual reorganization of the neural networks associated to memory. This process can last from hours to years, depending on the type of memory (Dudai, 2012; Frankland and Bontempi, 2005). After encoding, the reactivation of memory traces during subsequent waking state (Foster and Wilson, 2006; Karlsson and Frank, 2009; Sirota and Buzsaki, 2005) or slow-wave sleep (Diekelmann and Born, 2010; Wilson and McNaughton, 1994) may be particular important for memory consolidation. It has been shown in humans that the presentation of cues related to previously encoding episodes during periods of awake rest or sleep generates patters of activity in the hippocampus that are consistent with the reactivation of neuronal memory, and strengthens subsequent episodic memory for these episodes (Alm et al., 2019; Rasch and Born, 2007; Tambini et al., 2018).

A considerable amount of evidence has shown that consolidated memories can return to unstable (fragile) states when they are reactivated during retrieval or by a reminder cue (Dudai, 2012). Memory reconsolidation is the process that re-stabilizes the consolidated, existing memories after their reactivation (Sandrini et al., 2015). During this time-limited

reconsolidation window, consolidated memories can be modified (e.g. weakened, strengthened or updated) through behavioural means, pharmacological or non-invasive brain stimulation interventions (Elsey et al., 2018; Lee et al., 2017; Sandrini et al., 2018; Sandrini et al., 2015).

How can we non-invasively study memory processes in humans? Most behavioral and neuroimaging experiments on episodic memory consist of two phases (Fletcher and Henson, 2001)

1) Study phase (encoding) during which multiple single or pairs of stimuli are presented with or without instructions to remember them.
2) Test phase (retrieval) during which the stimuli presented during the study phase must be recalled or recognized after an interval of time (minutes, hours or days).

Episodic memory shows the largest degree of age-related decline (Rönnlund et al., 2005; Vestergren and Nilsson, 2011). Neuroimaging studies in older adults have shown that episodic memory decline is related to structural and functional brain changes (Daselaar and Cabeza, 2008; Nyberg et al., 2012; Sala-Llonch et al., 2014). Relative to younger adults, older adults tend to perform more poorly on free recall and recognition memory. The age difference in memory performance is larger for recall than recognition tasks (Jaroslawska and Rhodes, 2019). There is also evidence that associative memory (i.e. associations between items, such as face-name or object-location pairs) is more vulnerable to ageing than single-item memory (Old and Naveh-Benjamin, 2008).

Subjective memory complaints (SMC) without objective memory impairments are common in older adults (Bajo et al., 2012; Geerlings et al., 1999; Jorm et al., 1994; Vannini et al., 2017). Recent evidence have shown that older adults with subjective memory complaints (SMC) are at risk of developing amnestic Mild Cognitive Impairment (MCI) in the future (Jonker et al., 2000; Mitchell et al., 2014; Reisberg and Gauthier, 2008). According to Petersen et al. (2014), the criteria for a diagnosis of amnestic MCI are: subjective memory complaints corroborated by an informant, preserved everyday activities, memory impairment based on standard neuropsychological tests, preserved global cognitive functions, and lack of dementia. In most individuals, amnestic MCI represents a prodromal form of Alzheimer's disease (AD) (Petersen and Negash, 2008). AD is a neurodegenerative disease that causes a slow cognitive decline serious enough to interfere with daily life activities. One of the most common symptoms of AD is episodic memory loss. The incidence of AD is expected to increase as life expectancy growths across populations (Reitz and Mayeux, 2014). Because AD can produce tremendous chronic burdens on individuals, families, and health care

systems around the world, there is a critical need to develop effective interventions to prevent/delay the onset of AD (i.e. primary or secondary prevention) or slow the worsening of symptoms and improve quality of life (Buschert et al., 2011; Manenti et al., 2012a). Because pharmacological interventions have failed to show efficacy in clinical trials with mild to moderate AD (Karakaya et al., 2013), there is a critical need to develop alternative, effective interventions. Transcranial electrical stimulation (tES) (Antal et al., 2017; Dayan et al., 2013; Woods et al., 2015) has become a promising method to improve long-term memory function in health and disease (Buch et al., 2017; Hsu et al., 2015; Miniussi et al., 2013; Sandrini and Cohen, 2013).

Here, we critically review studies investigating whether tES may improve episodic memories in heathy older adults and in patients with MCI or AD. Specifically, we included studies that used at least one episodic memory test.

2. Transcranial electrical stimulation

Since the studies evaluating the effects of tES on episodic memory in physiological and pathological ageing have used transcranial direct current stimulation (tDCS) or slow oscillation tDCS (so-tDCS), we will briefly describe these two techniques (Bikson et al., 2019).

tES aims to modify brain function noninvasively by delivering current to electrodes on the scalp. Conventional tDCS is a tES technique which uses sustained direct current applied to the head via two electrodes (anode and cathode) with current intensities between 1 and 2 milliAmpere (mA). Electrode position on the scalp (and body for extracephalic electrodes) are generally defined using to the 10–20 EEG international system (e.g. electrode position F3 for the left DLPFC) or anatomical landmark (e.g. “supraorbital”). The duration of stimulation is typically 5-30 minutes. The electrodes are generally 5x5 cm or 5x7 cm, though smaller and larger electrodes are also utilized. Isotonic saline (saturated in a sponge) or gels and/or creams are used to provide low-impedance contact with the skin (Fonteneau et al, 2019). In sham tDCS condition, the current is turned off typically 10-20 seconds after the beginning and is turned on at the end of the stimulation period so that the participants cannot distinguish between active and sham stimulation (Fonteneau et al., 2019).

Slow oscillations tDCS (so-tDCS) conventionally refers to a signal with a frequency below 1 Hz (e.g. 0.75 Hz) (Fonteneau et al., 2019). The on-off time of so-tDCS may be varied (e.g. 5 intervals with 1 min gap (Eggert et al., 2013).

It has been shown that the primary acute effects of tDCS derive from a shift of membrane potential, which are influenced by electrical current direction relative to neuronal orientation. Anodal tDCS increases neuronal excitability by causing a depolarization of the resting potential, while the cathodal tDCS hyperpolarizes the resting potential, thus suppressing neuronal excitability (Dayan et al., 2013; Fonteneau et al., 2019). The after-effects require synaptic plasticity. Prolonged membrane polarization by tDCS changes neuroplasticity through N-Methyl-D-aspartic acid (NMDA) receptors, thereby leading to long-lasting after-effects of tDCS (Fonteneau et al., 2019; Roche et al., 2015). Another explanation relies on the modification of brain neurometabolites (Pini et al., 2018; Roche et al., 2015). The concentration in GABA and glutamatergic metabolites (Glu/glutamine, Glx) can be measured in vivo using magnetic resonance spectroscopy (MRS) (Zhu et al., 2011). Most of the studies investigated metabolites changes in the motor cortex and found a reduction of GABA after active (anodal) tDCS (Bachtiar et al., 2015; Lee et al., 2015; Stagg et al., 2011). It has been shown that age may modulate the effect of tDCS on metabolite concentration. Antonenko et al. (2017) reported a reduction of GABA levels after anodal tDCS relative to sham stimulation, reflecting the preserved neuromodulatory effect of active tDCS in older adults. Beyond these local effects, the combination of tDCS with neuroimaging techniques has shown interactions between interconnected brain regions beyond the targeted cortical area (Pini et al., 2018; Venkatakrishnan and Sandrini, 2012). A study combining PFC-tDCS with large-scale neurophysiological recordings from monkeys showed improvement of memory performance. While firing rates did not change within the stimulated area, tDCS induced large low-frequency oscillations in the underlying tissue (Krause et al., 2017). These findings are consistent with the observation that tDCS induces functional changes by dynamic modulation of functional connectivity (Keeser et al., 2011; Meinzer et al., 2015; Pena-Gomez et al., 2012; Reinhart and Woodman, 2015).

3. Effects of tDCS in physiological ageing

3.1 Episodic memory for verbal information

Manenti et al. (2013) conducted a study to investigate the effects of tDCS with the anode over the dorsolateral prefrontal cortex (DLPFC) or posterior parietal cortex (PPC) on retrieval of verbal episodic memory in healthy young and older adults. During the encoding phase, participants had to decide if the word presented on the screen was an abstract or concrete word. After 5 minutes delay, participants had to indicate if the displayed words was “old” or

“new” (recognition task). The authors observed that, relative to sham, active tDCS with the anode over the left and right regions (DLPFC and PPC) induced better recognition performance in young adults. Only active tDCS applied over the left brain areas (DLPFC and PPC) increased recognition memory relative to sham stimulation in older adults. This finding may be consistent with a material specific-model, which postulates that the left hemisphere is engaged in verbal memory processes and the right hemisphere is involved in visuospatial memory processes (Golby et al., 2001; Wagner et al., 1998). The authors interpreted the selective involvement of the left areas during the retrieval of abstract and concrete words in older individuals as an expression of a primary use of verbal code and an inefficient mental imagery strategy, in line with the idea that the capacity to generate non-verbal mental image strategies declines with age (Dror and Kosslyn, 1994; Manenti et al., 2011). Accordingly, the asymmetrical left facilitation observed in older adults were interpreted as reflecting a loss of regional specialization or declining specificity, referred to a dedifferentiation process, which has been assumed to occur in ageing (Goh et al., 2010; Park et al., 2004; Park and Reuter-Lorenz, 2009). Remarkably, in a subsequent study, Brambilla et al. (2015) re-analyzed data acquired in the previous study (Manenti et al., 2013) in order to clarify whether the recorded different hemispheric recruitment in young and in elderly individuals may be beneficial to maintaining memory performance in older adults or, instead, if it may represent evidence of brain dysfunction. The results of this reanalysis showed a direct correlation between the bilateral engagement of DLPFC and PPC regions and memory and executive functions. Specifically, young individuals and high-performing older adults exhibited similar performances on episodic memory tasks along with symmetrical recruitment of left and right areas, whereas low-performing older adults demonstrated a greater engagement of the left hemisphere during verbal memory task. These findings drew attention to brain maintenance hypothesis (Nyberg et al., 2012), according to which less structural brain change is associated with better memory performance in old age.

On the basis of the above findings (Manenti et al., 2013), Sandrini et al. (2014) applied active tDCS with the anode over the left DLPFC in a protocol used to study episodic memory reconsolidation in young adults (Sandrini et al., 2013). On Day 1, older adults learned a list of 20 words. Twenty-four hours later (Day 2), they received a contextual reminder (same experimenter and same experimental room of Day 1). In young adults existing memories are automatically reactivated if the participants return to the same experimental room of Day 1 (Hupbach et al., 2008). Stimulation (active or sham) was applied after an interval of 10

minutes. It has been shown that the reconsolidation process begin between 3 and 10 minutes after memory reactivation (Monfils et al., 2009). To determine if the effect was due to reactivation, a third group of participants received active tDCS without a contextual reminder (different experimenter and different room). Free recall was tested on Day 3 (48h after the learning session) and Day 30 (1 month after the learning session). Surprisingly, active tDCS (i.e. with or without reminder) strengthened existing verbal episodic memories, an effect indicated by enhanced memory recall up to 1 month, compared to sham stimulation. Unlike the young adults (Sandrini et al., 2013), being in the same hospital might have been more salient to older adults than the distinction between the two experimental rooms, and the no reminder group would have been reminded of the learning session (Day 1) and performed the same as the reminder group. It has also been shown that older adults have poor memory for the source and problems with the process of binding memories so that contextual cues may be encoded but may not be properly bound to the specific episode (Chalfonte and Johnson, 1996; Naveh-Benjamin and Craik, 1995; Sandrini et al., 2014; Schacter et al., 1991). Furthermore, Kroes and colleagues (Kroes et al., 2014) applied electroconvulsive therapy in patients with unipolar depression and observed memory reconsolidation impairment, despite a change of room in the hospital. These findings emphasize the strength of the hospital context for allowing memory reactivation.

Using a similar protocol, Manenti et al. (2017) applied active tDCS with the anode over the left DLPFC in older adults with SMC, a population at risk of developing aMCI. Participants obtained scores of more than 1.0 standard deviation (SD) at Everyday Memory Questionnaire (Calabria et al., 2011) relative to the mean score obtained in a group of healthy older adults (Manenti et al., 2016). In addition, they had normal objective cognitive performance in all the administered tests, and absence of mood and anxiety disorders. The difference with the above study (Sandrini et al., 2014) was the presence of recognition tasks (old/new) after free recall tests on Day 3 and Day 30. The results showed that active tDCS enhanced recognition memory (discrimination accuracy) up to 30 days relative to sham stimulation. The behavioral effects observed only in the recognition tasks suggest that the familiarity component is relatively maintained in the ageing process, whereas recollection shows age-related impairment (Danckert and Craik, 2013). The effect of active tDCS in SMC might be related to a facilitation of the access to memory trace. A number of studies supported the hypothesis that word recall failure reflects intratrial forgetting, which refers to the decay of traces during the time between the presentation and the requested recall of an item (Tulving, 1964). One possibility is that memory trace would be available, but not

accessible for recall. A considerable body of evidence confirms that retrieval success is closely related to the number and quality of the available retrieval cues (Hunt and Smith, 1996; Tulving and Pearlstone, 1966). The difference with a previous study (Sandrini et al., 2014) could be also due to sample size: too small to detect differences in recollection in SMC. Of note, on day 3 the mean percentage of words correctly recalled was 21.8% (SD 12.3) in the active group and 14.1% (SD 9) in the sham group. This study shows for the first time that recognition memory can be enhanced, conceivably through reconsolidation, in older adults with SMC.

For learning and memory formation, synchronized task- and stimulation-induced plasticity might be critical. In this case, tDCS might enhance task-related activity (Martin et al., 2014; Shin et al., 2015). Medvedeva et al. (2019) applied active tDCS with the anode over the left ventrolateral prefrontal cortex (VLPFC) during the encoding phase. Older adults were asked to try to memorize each word for a subsequent recognition memory test (24h later). Discrimination accuracy was higher in participants in the anodal tDCS group relative to the sham group. There was no difference between the two groups in hits and false alarm rates, response bias or response times. This facilitation effect was also evident in young adults, in which memory was tested after a delay of 1h. Memory performance was unaffected by offline administration before encoding or retrieval in young adults. This suggest that, at least in the episodic memory domain and the left VLPFC, tDCS effects take place during the stimulation rather than after its termination.

Sandrini et al. (2016) applied active tDCS with the anode over the left DLPFC while older adults learned a list of 20 words. Free recall was tested on Day 3 (48h after the learning session) and Day 30 (1 month after the learning session). The results showed that active tDCS strengthened episodic memories, an effect indicated by enhanced delayed recall (48 hours) relative to sham tDCS. No effect was observed on Day 30, learning rate or number of words correctly recalled in the last learning trial. This study demonstrated off-line, but not effects, suggesting an interaction between tDCS and consolidation processes (Reis et al., 2009). This support the results of previous studies which systematically compared online and offline stimulation in other domains and found prominent offline effects (Pirulli et al., 2013; Santarnecchi et al., 2014), and contradicts episodic memory studies that found no offline effects of tDCS (Medvedeva et al., 2019). One possible explanation of this difference is that temporal specificity of tDCS that varies as function of the involvement of the stimulated brain region during a specific stage of processing and associated cognitive functions. Another possibility may be due to different stimulation parameters and electrode

montage used in these studies (see Table 1). In addition, recent meta-analytic evidence suggests that offline effects of tDCS are stronger than online effects when used in older adults (Hsu et al., 2015).

To determine whether tDCS applied immediately after verbal encoding is able to interact directly with the consolidation processes, Sandrini et al. (2019) applied active tDCS with the anode over the left DLPFC immediately after the encoding phase in healthy older adults. Participants learned a list of 20 words. Free recall was tested on Day 3 (48h after the learning session) and Day 30 (1 month after the learning session). The results shows that, relative to sham stimulation, active tDCS applied immediately after encoding enhanced episodic memory recall at 1 month. The current work supports the conclusion that stabilization of episodic memories may be facilitated by direct interaction of tDCS with the mechanisms of consolidation. In support of these findings, a recent study showed that tDCS applied with the anode over the primary motor cortex immediately after training enhanced motor memory consolidation in healthy older adults (Rumpf et al., 2017).

Antonenko et al. (2019) conducted a study in older adults where they aimed to modulate episodic memory formation using active tDCS with the anode over left temporoparietal cortex. Participants were asked to learn novel associations between pictures and pseudowords during five learning blocks while they received tDCS. Episodic memory performance was tested during immediate retrieval. During retrieval blocks, learning success was assessed in a “transfer” task (generalization effects). Instead of presenting a picture, corresponding German spoken words were presented with the pseudowords. Percentage of correct responses and mean reaction time of each block were assessed. The primary outcome measure for episodic memory performance was the percentage of correct responses during the immediate retrieval block. The results showed that older adults retrieved significantly more correct pairings of newly acquired picture-pseudoword associations in the transfer task. Participants also showed steeper learning curves during active relative to sham tDCS. These findings extend previous results from young adults (Floel et al., 2008) to the ageing population. For example, Flöel et al. (Floel et al., 2008) found accelerated learning and improved retrieval of newly acquired picture-word pairs when learning was accompanied by active tDCS, using identical task and stimulation parameters. In addition, prior the tDCS experiment, participants underwent resting-state functional magnetic resonance imaging (rs-fMRI). Functional connectivity between left hippocampus and left temporoparietal brain area resulted positively related to initial memory performance, and positively associated with the magnitude of individual tDCS-induced memory

enhancement. These findings supports evidence that functional connectivity at rest can be used as a predictor for individual response to noninvasive brain stimulation (Hordacre et al., 2017; Tambini et al., 2018).

3.2 Episodic memory for nonverbal information

Long-lasting positive effects on episodic memory have been also observed for non-verbal information (Antonenko et al., 2018; Flöel et al., 2012).

Flöel et al. (2012) applied active tDCS with the anode over the right temporoparietal cortex during an object location memory task, in which subjects acquired the correct position of buildings on a street map. The results showed enhanced recall up to 1 week (offline effect) after active tDCS relative to sham stimulation. No behavioural effects were observed on the learning curve and immediate free recall (online effect). These findings are consistent with previous studies showing that tDCS enhanced offline, but not online effects (Flöel et al., 2012; Reis et al., 2009; Sandrini et al., 2016; Santarnecchi et al., 2014), supporting the idea that consolidation processes are susceptible to active tDCS (Sandrini et al., 2019).

Antonenko et al. (2018) investigated the neuronal and behavioral effects of active tDCS applied with the anode over the right temporoparietal cortex during object-location memory training on 3 consecutive days in young and older adults. Participants were asked to learn the correct object-location pairings on a street map. Resting state-fMRI (rs-fMRI) was conducted at baseline and at 1-day after training. At the behavioral level, the results showed that anodal tDCS enhanced memory recall, assessed 1 day after training, relative to training alone (sham stimulation). No effect on memory recall was observed for the trained material at 1 month. During this follow-up assessment active tDCS induced transfer effects (generalization) on a different version of the training task and a verbal episodic memory task compared to sham tDCS. Such transfer effects have been shown in adults after active tDCS-accompanied training schedule on far transfer tasks (Jones et al., 2015; Stephens and Berryhill, 2016), even in the absence of effects in the trained older task or near-transfer tasks (Stephens and Berryhill, 2016). Young adults performed better than older adults in all test sessions. These findings are in line with previous studies of multi-day combinations of cognitive training with tDCS in young adults (Au et al., 2016; Meinzer et al., 2014; Ruf et al., 2017) and expand previous results of single-session studies on episodic memory in older adults (Flöel et al., 2012; Sandrini et al., 2016).

At the neuronal level, they authors analysed functional connectivity in the default mode network (DMN). DMN is a well-established large-scale neural network mediating episodic

memory function (Jeon et al., 2016; Jeong et al., 2015). Declines in DMN connectivity have been shown in physiological and pathological ageing (Jones et al., 2011). The results showed that intrinsic DMN functional connectivity increased after training in the active tDCS group. The findings suggests that rs-fMRI assessing intrinsic functional brain activity may be a biomarker and diagnostic tool for physiological and pathological ageing (Ferreira and Busatto, 2013; Salami et al., 2014) as well as for the investigation of changes induced by the intervention (Kobe et al., 2017).

Another promising approach to prolong the beneficial effects is the combination of selective serotonin reuptake inhibitor (SRRI) and tDCS. Blocking the serotonin transporter with SSRI increases the level of serotonin available in brain areas (Invernizzi et al., 1997).

Previous work revealed that increasing serotonin levels might enhance tDCS-induced neuroplasticity (Kuo et al., 2016; Nitsche et al., 2009). Prehn et al. (2017) examined for the first time the effect of active tDCS applied with the anode over the right temporoparietal cortex during an object-location learning task with a single dose of citalopram (drug intake 2h before the task). The learning session consisted of 3 learning blocks and was followed by immediate (primary outcome) and 3 delayed cued recall tasks (6h, 1 day and 1 week). Young and older adults performed the memory task in each of the four conditions: sham tDCS+placebo, sham tDCS+SSRI, active tDCS+placebo, and active tDCS+SSRI. The results showed an effect of medication but no significant effect of tDCS on immediate recall scores. However, young and older adults benefited most from the combined application (comparisons: active tDCS+SSRI > active tDCS+placebo and active tDCS+SSRI > sham tDCS+placebo). No effects were found on delayed cue recall tasks. These findings are in contrast to Nitsche et al (2009), who demonstrated that under placebo medication, anodal tDCS enhanced motor cortex excitability for about 60-120 min. Citalopram enhanced and prolonged the facilitation induced by anodal tDCS. Moreover, Kuo et al (2016) found that chronic application of citalopram increased and prolonged the LTP-like plasticity induced by anodal tDCS for over 24 h. The lack of an effect of active tDCS alone on delayed memory performance (active tDCS+placebo > sham+placebo) is also in contrast to a previous study from the same group (Flöel et al, 2012). According to the authors, differences in the paradigm and in the response format (three alternative forced choice vs free recall) may explain the differential results. In conclusion, these findings provide first evidence that tDCS enhances immediate memory performance if serotonergic neurotransmission is increased simultaneously, but these behavioural effects do not continue over time.

Although the studies reported so far show beneficial effects on episodic memory, there are findings that are inconsistent with the trend that tDCS effects are larger in healthy older than younger adults (Kulzow et al., 2017; Leach et al., 2019).

Leach et al. (2019) applied active tDCS with the anode over the left DLPFC during a face-name encoding task, and measured both cued recall and recognition performance. Young and older adults completed memory tests immediately and 24h after stimulation to observe both immediate and delayed tDCS effects on associative memory. The results showed that, relative to sham stimulation, active tDCS enhanced face-name associative memory for both recall and recognition measured immediately and after 24h in younger adults. These findings support previous studies that found tDCS effects on associative memory in younger adults (England et al., 2015; Gray et al., 2015). In addition, the results suggest that tDCS may enhance associative memory through offline stimulation effects as demonstrated in previous studies (Pirulli et al., 2013; Santarnecchi et al., 2014). No difference in memory performance was found between active and sham tDCS for older adults. The lone study finding associative memory improvement in older adults applied stimulation to a different region (tempoparietal; Flöel et al., 2012) than they used in this study.

Kulzow et al. (2017) explored the combined efficacy of tDCS and memory training. Older adults underwent a 3-day visuospatial training paired with active tDCS applied with the anode over the right temporoparietal cortex. Participants were asked to learn the correct object-location pairings on a street map. Acquisition performance was measured by accuracy on a given learning block in terms of percentage of correct responses. Training success (performance on last training day) and delayed memory after 1-month (long-term effects) was also assessed. In addition, transfer effects (generalization) on similar trained (visuospatial) and less similar (visuo-constructive, verbal) untrained memory tasks were explored, both immediately after training, and after 1-month. First, they found significant improvement in both training conditions, without additional gain induced by active tDCS in training success or delayed memory performance. The combined 3-day intervention of active tDCS and memory training did not induce beneficial effects on other trained and untrained memory tasks.

While a previous study from the same team found beneficial effects of combined intervention on objects-location memory performance (Antonenko et al., 2018), this study did not find a positive effect on training success. According to the authors, there were differences between the two studies. The way training success was measured, and the different test formats and time of testing (immediate vs. delayed) might partly explain the inconsistent results. In

addition, results from between-subject design (Antonenko et al., 2018) might contradict results from within-subject design (cross-over), (Kulzow et al., 2017) particularly because of possible carry-over effects.

In summary, most of the studies showed beneficial effects on verbal and nonverbal episodic memory using tDCS with the anode over the lateral prefrontal cortex or temporoparietal cortex, respectively (see Figure 1 for timing of stimulation and Table 1 for parameters of stimulation). A single session of tDCS may induce long-lasting effects (24h up to 1 month) (Flöel et al., 2012; Manenti et al., 2018; Manenti et al., 2017; Medvedeva et al., 2019; Sandrini et al., 2014; Sandrini et al., 2016; Sandrini et al., 2019). Multiple sessions of tDCS may induce generalization (Antonenko et al., 2018). tDCS may enhance memory performance if serotonergic neurotransmission is increased simultaneously (Prehn et al., 2017). Memory retrieval performance may be facilitated through an interaction of tDCS with the mechanisms of consolidation or reconsolidation (Floel et al., 2012; Manenti et al., 2018; Manenti et al., 2017; Sandrini et al., 2014; Sandrini et al., 2016; Sandrini et al., 2019). At the neuronal level, intrinsic functional connectivity in the DMN may be increased after tDCS (Antonenko et al., 2018). Functional network coupling at rest may predict individual response to tDCS (Antonenko et al., 2019).

4. Effects of so-tDCS during sleep in healthy ageing and MCI

Sleep is thought to play an important role in long-term consolidation of memory (Diekelmann and Born, 2010). Slow oscillatory activity (<1 Hz) and sleep spindles (8-15 Hz), which can be measured by electroencephalography (EEG), seem to be critical for declarative memory (Schabus et al., 2004). When newly encoded memories are reactivated during sleep, sharp-wave ripples (80-100 Hz) in the hippocampus and sleep spindles trigger extracellular mechanisms that increase synaptic plasticity, critical for consolidation to occur (Sejnowski and Destexhe, 2000). Reactivated information is then redistributed to cortical storage networks by waves of slow oscillations that coordinate the firing of sharp-wave nipples and spindle activity (Clemens et al., 2007; Fogel and Smith, 2011). Essentially, new acquired information can be transferred from an unstable state within the hippocampus into a more stable state within the neocortex, and are incorporated into pre-existing memory traces over time by hippocampal-neocortical interactions mediated by slow oscillations (Diekelmann and Born, 2010). There is evidence that slow oscillations are generated by prefrontal regions

(Massimini et al., 2004). Some studies have causally implicated slow-wave oscillations in memory consolidation (Garside et al., 2015; Marshall et al., 2006; Marshall et al., 2004). Marshall et al. (2006) applied active slow oscillation-tDCS (so-tDCS) (0.7-0.8 Hz) with two anodes positioned bilaterally over prefrontal areas during nocturnal sleep in young adults. They demonstrated that the application of so-tDCS improved episodic memory (i.e. recall of word-pairs) after sleep relative to sham so-tDCS. In addition, EEG demonstrated enhanced slow oscillations activity as well as density of frontal slow sleep spindles.

Since changes in sleep (i.e. decrease in slow wave oscillations, frontal slow wave activity) are well-documented in ageing, the findings of the study reported above opens the possibility that so-tDCS can boost slow oscillations activity and enhance episodic memory consolidation in older adults.

Using the procedure developed by Marshall et al., (2006; 2004), Westerberg et al. (2015) applied active so-tDCS (0.75 Hz) during an afternoon nap in older adults. Memory was tested before and after sleep. Three memory tests were administered: two declarative memory tests (word-pairs recall; fact recognition) and a non-declarative object-priming test. The results revealed an improvement in the recall of word-pairs and higher slow wave activity in the active so-tDCS relative to sham stimulation. This study showed for the first time that this procedure may improve episodic memory in healthy older adults. In addition, it shows that so-tDCS can be applied during a nap, therefore avoiding inconveniences caused by nocturnal stimulation, such as stress due to testing during late evening and an unfamiliar environment during sleep.

Ladenbauer et al. (2017) investigated for the first time the effect of so-tDCS (0.75 Hz) applied with two anodes positioned bilaterally over prefrontal scalp locations during an afternoon nap on visuospatial memory task (picture memory and location memory). In addition, they evaluated also verbal memory (word-pairs). EEG activity was recorded during the nap and the immediate effects of so-tDCS on brain activity were assessed. The results showed that picture memory was improved after sleep and frontal slow oscillatory activity as well as fast spindle activity increased in the anodal so-tDCS compared to sham stimulation. Relative to previous studies (Marshall et al., 2006; Westerberg et al., 2015), the current study did not find an effect on verbal episodic memory in older adults. According to the authors, differences in the verbal task relative to the one used by Marshall et al. (2006), such as the presence of non-emotional category-instance pairs and strong semantic association in the word-pairs, might have prevented an effect of so-tDCS.

It has been shown that sleep, especially slow oscillations, promotes the clearance of cortical amyloid-beta peptide (Xie et al., 2013), which is involved in the pathogenesis of AD. Ladenbauer et al. (2017) addressed the question whether patients with MCI, who suffer severe impairments in sleep and memory and at risk of developing AD, would benefit from so-tDCS during sleep in terms of EEG-derived sleep characteristics (i.e. slow oscillations, spindle activity and cross-frequency coupling) and episodic memory performance. Using the protocol described previously by (Ladenbauer et al., 2016), the authors showed increased overall slow oscillations and spindle power, and for the first time the coupling of slow oscillations to spindle activity, a component considered critical for the transfer of episodic memories from hippocampus to neocortex. In addition, visuospatial memory performance was improved by active so-tDCS relative to sham stimulation and was associated with stronger synchronization between slow oscillations and fast spindle power (Ladenbauer et al., 2017). As in previous study (Ladenbauer et al., 2016), they did not find any effects of so-tDCS in location memory and verbal memory tasks. This study showed the potential of so-tDCS to enhance functional relevant sleep parameters and improve visual recognition memory in amnestic MCI.

Although the studies reviewed so far showed improvements in episodic memory, some studies did not find any or even contrasting effects (Eggert et al., 2013; Paßmann et al., 2016). Eggert et al. (2013) investigated the effects of so-tDCS (0.75 Hz) applied with two anodes positioned bilaterally over prefrontal locations during nocturnal sleep in older adults. The results showed that, independent from stimulation condition (anodal and sham), overnight retention performance decreased in a word-pairs task. In addition, stimulation failed to show modulations in sleep oscillations. According to the authors, possible explanations for the conflicting results may be due to some differences in stimulation protocol. The authors introduced a current ramping at the beginning and at the end of each stimulation interval, which might have prevented entrainment of slow oscillatory activity by so-tDCS. Compared to Marshall et al. (2006), differences in applied current and the type of electrodes (non-sintered vs sintered) may have affected the findings of this study.

Paßmann et al. (2016) applied so-tDCS (0.75 Hz) with two anodes positioned bilaterally over prefrontal scalp locations during early nocturnal slow wave sleep in older adults. The results showed that, relative to sham stimulation, anodal so-tDCS increased slow wave and spindle activity immediately flowing stimulation. These findings were accompanied by impaired visuospatial memory consolidation. No effect was detected on verbal memory performance (word-pairs). According to the authors, these behavioral findings are possibly explained by

a decline in slow wave oscillations over the entire night that may have prevented and reversed the positive effect of so-tDCS.

In summary, three studies showed a beneficial effects of a single session of so-tDCS during sleep on episodic memory. While Westerberg et al. (2015) found an effect on verbal memory (word-pairs) in older adults, Landenbauer et al., (2016; 2017) demonstrated effects on visuo-spatial memory (picture memory) in older adults and MCI (See Table 1 and 2). Two studies reported impaired memory performance in older adults (Eggert et al., 2013; Paßmann et al., 2016). These studies support the resutls of a meta-analysis indicating that tES applied during sleep modulates declarative, but not procedural, memory consolidation (Barham et al., 2016). At the neuropsysiological level, these behavioral findings were accompanied by changes in slow oscillations power (Ladenbauer et al., 2016; Ladenbauer et al., 2017; Paßmann et al., 2016; Westerberg et al., 2015) and spindle activity (Ladenbauer et al., 2016; Ladenbauer et al., 2017; Paßmann et al., 2016). In addition, so-tDCS enhanced endogenous slow oscillations-to-spindle coupling (Ladenbauer et al., 2017).

Insert Figure 1 about here

Insert Table 1 about here

5. Effects of tDCS in MCI

Yun et al. (2016) examined the effects of multiple sessions of active tDCS applied over the DLPFCs in subjects with aMCI. Before and after the intervention (three times per week for 3 weeks) participants underwent cognitive testing and positron emission tomography (PET). The results showed that multiple sessions of active tDCS increased regional cerebral metabolism measured with PET relative to sham stimulation. Specifically, they found increased 2-deoxy-2-[F18] fluoro-D-glucose (FDG) uptake in multiple brain regions, including the anterior and posterior insular, hippocampal, and parahippocampal regions, especially in the active tDCS group In addition, subjective memory satisfaction and enhancement of memory strategies of aMCI patients were observed only in the active group. Previous studies also showed that tDCS increased the brain metabolism as compared with sham stimulation (Paquette et al., 2011; Yoon et al., 2014).

Murugaraja et al. (2017) tested the effects of five sessions of active DCS with the anode over the left DLPFC in subjects with aMCI. In this open label study, picture memory impairment was tested before tDCS, 3 minutes (immediate recall) and 20 minutes (delayed

recall) after the administration of the final tDCS session and 1 month after the day of the final tDCS session. The results showed that five consecutive sessions significantly improved immediate and delayed recall of pictures over an extended period of 1 month. These findings need a replication with a better methodology (i.e., randomized and sham controlled trial).

Using the same protocol of a previous study (Manenti et al., 2017), Manenti et al. (2018) applied active tDCS with the anode over the left DLPFC in a pilot study with aMCI. Older adults with aMCI learned a list of 20 words. Twenty-four hours later, tDCS (active or sham) was applied after a contextual reminder. Memory retrieval (free recall and recognition) was tested 48h and 1 month after the learning session. The results showed for the first time that active tDCS enhanced recognition abilities, conceivably through reconsolidation, relative to sham stimulation in older adults with aMCI. No effects were found on free recall or on hits and false-alarm rates. As in a previous study with SMC (Manenti et al., 2017), the results showed that recognition memory, rather than delayed recall, was enhanced by active tDCS. These findings support studies that showed improved recognition memory in AD (Ferruci et al., 2008; Boggio et al., 2012). The effect of active tDCS might be related to a facilitation of accessibility of the memory trace. Although delayed recall was not significantly different between the two groups (active vs sham), an impairment in this function is one of the core characteristics of aMCI and early AD. Lack of effect on delayed recall were also found after multiple sessions of tDCS over the same region in early AD (Im et al., 2019). Because aMCI is associated with large decline in recollection (Koen and Yonelinas, 2014), tDCS might have a facilitation effect on a task that is thought to depend more on familiarity (recognition) than recollection (recall). Future work is needed to determine whether the tDCS effect on recognition could have a clinical impact, since enhanced ability to recall information would have greater impact on daily living than improved ability to recognize.

Gomes et al. (2019) applied multiple sessions of active tDCS with the anode over the left DLPFC in individuals with MCI. In this pilot study, participants were evaluated before and after the treatment (tDCS applied for 30 minutes for 10 sessions, twice a week) by a battery of cognitive tests, including the Word List Memory Test (WMT). In this test, individuals were presented 10 words and had to recall them after 90 seconds and to recognize them from among 10 other distractors after 15 minutes (Atkinson and Shiffrin, 1971). The results showed improvement in memory recall, verbal fluency and executive functioning in the anodal tDCS group relative to sham group. Since they applied many multiple comparisons, instead of using Fisher's LSD, the statistical analysis should employ more conservative methods for multiple comparison corrections such as Bonferroni.

Fileccia et al. (2019) examined the effects on cognition of multiple-sessions of active tDCS with the anode over the left DLPFC in subjects with MCI. The protocol consisted in 20 minutes, 5 days per week of tDCS (up to a total of 20 days). Participants underwent neuropsychological evaluation at baseline and immediately after the last day of stimulation. Episodic memory was assessed with the Rey Auditory Verbal Learning test (RAVLT). The results showed that, relative to baseline and sham groups, participants who received active tDCS improved in episodic memory (RAVLT: immediate recall) and in figure naming test. One limitation of this study is the lack of long-term follow-up.

Lu et al. (2019) applied tDCS and working memory training (WMT) to enhance cognitive functions in individuals with MCI. tDCS was applied with the anode over left lateral temporal cortex (LTC). The rationale for selecting LTC was that medial temporal lobe (MTL), including hippocampus, is the primary region affected in late onset AD (Dickerson et al., 2004). Because MTL is difficult to reach through noninvasive brain stimulation, LTC, as the "surface" part of MTL, engages a disease-specific spotlight here (Ezzyat et al., 2018). Participants were assigned for a 4-week intervention (3 sessions per week) of either a combination of tDCS and WMT (adaptive n-back task), sham tDCS and WMT, or tDCS and control cognitive training (CCT, continuous performance test). Stimulation was applied with the anode over the left lateral temporal cortex. The primary outcome measures were working memory performance and global cognitive function measured by the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog). The secondary measures were category verbal fluency test, trail making test, logical memory, and word list learning test. The assessments of these functions were conducted at baseline (T0), post-intervention (T1), 4 weeks post-intervention (T2) and 8 weeks post-intervention (T3). Cognitive enhancement was found across all the groups after the intervention. The group that received the combination of tDCS and WMT showed significantly greater improvement relative to single-modality groups in delayed recall memory and working memory capacity post-intervention, and logical memory at T3. However, the lack of a control group (i.e tDCS and control cognitive training) may have affected the interpretation of the treatment efficacy. These findings support previous studies showing enhancement of memory with tDCS combined with training (Park et al., 2014; Richmond et al., 2014; Ruf et al., 2017; Stephens and Berryhill, 2016).

Although the study reviewed so far showed positive effects of tDCS on episodic memory, a recent study showed negative effects. Das et al. (2019) investigated the effects of active tDCS with the anode over the left VLPFC combined with gist-reasoning training (SMART)

versus sham tDCS plus SMART on cognition and neural changes in resting cerebral blood flow (rCBF). Eight SMART sessions were administered over 4 weeks with tDCS for 20 minutes before each SMART session. SMART has been shown to be beneficial in MCI (Mudar et al., 2017; Mudar et al., 2019). Patients with MCI were assessed immediately and 3-months after the intervention. The results showed cognitive gains immediately after training on episodic memory, inhibition and innovation in the sham tDCS + SMART, but not in the active tDCS + SMART. The gains did not last for 3 months after the intervention. At the neuronal level, a voxel-based analysis revealed increase in region rCBF in the right DLPFC in active tDCS + SMART relative to sham tDCS + SMART. The findings of this study suggests that active tDCS "blocked" rather that enhanced certain cognitive functions. According to the authors, a possible explanation for this behavioural effect is the timing of application of tDCS: in previous studies tDCS was applied during learning (Antonenko et al., 2019; Antonenko et al., 2018; Flöel et al., 2012; Sandrini et al., 2016) while in the current study tDCS was applied before the training.

In summary, most of the studies showed beneficial effects on episodic memory when active tDCS is applied with the anode over left DLPFC, supporting previous studies that targeted the same region in healthy older adults (Manenti et al., 2013; Sandrini et al., 2016; Sandrini et al., 2019). One study found improvement after tDCS was applied over LTC (Lu et al., 2019) (see Table 2 and Figure 2). Most of these studies used multiple-sessions of tDCS to induce long-lasting effects (Fileccia et al., 2019; Gomes et al., 2019; Yun et al., 2016). Only one study found long-lasting effects when a single tDCS session was applied conceivably through the reconsolidation process (Manenti et al., 2018). Only four studies assessed long-term effects of the intervention (Das et al., 2019; Gomes et al., 2019; Lu et al., 2019; Murugaraja et al., 2017). At the neuronal level, tDCS has been shown to increase the regional cerebral metabolism in multiple brain regions, including the insular, hippocampal, and parahippocampal regions (Yun et al., 2016).

Insert Table 2 about here

6. Effects of tDCS in Alzheimer's disease

Given the limited effectiveness of pharmacological treatments, non-pharmacological interventions to slow the worsening of symptoms of AD have gained attention in recent years.

Ferrucci et al. (2008) tested recognition memory and visual attention before and 30 minutes after one session of active tDCS with the anode or the cathode over the temporoparietal areas in patients with AD. The data showed that word recognition memory task performance improved after active tDCS with the anode over the temporoparietal areas, whereas it worsened after active tDCS with the cathode over the temporoparietal areas and it remained unchanged after sham tDCS, suggesting that tDCS over the temporoparietal areas can modify memory in patients with AD. In line with these results, Boggio et al. (2009) investigated the effect of active tDCS with the anode over two different target areas (left DLPFC or left temporal cortex) compared to sham tDCS on recognition memory, working memory and selective attention in patients with AD. Stimulation was applied during these cognitive tasks in three experimental sessions corresponding to the tDCS conditions. The results showed a selective improvement in visual recognition memory during temporal and prefrontal tDCS relative to sham stimulation, indicating that active tDCS with the anode over both the left DLPFC and the left temporal cortex can increase memory performances in AD. In order to test the hypothesis that repeated sessions of tDCS could induce long-term effects, a few single case studies without a control tDCS condition suggested that repeated application of active tDCS could be useful in stabilizing (Andrade et al., 2016; Bystad et al., 2017) or improving (Bystad et al., 2016) episodic memory in patients with AD. Interestingly, in a cross-over single-case study, Penolazzi et al. (2015) assessed the effects of two different cycles of treatments (active tDCS followed by cognitive computerized tasks and sham tDCS followed by cognitive computerized tasks) on the Brief Neuropsychological Examination (ENB 2) (Mondini, 2011) including subtests for short-term memory, working memory, episodic memory, attention, visuospatial abilities and constructional apraxia on a patient with AD. The results revealed that active tDCS plus cognitive training cycle slowed the cognitive decline of the patient's cognitive functioning lasting approximately 3 months. In particular, at the active tDCS plus cognitive training cycle an improvement in working memory, attention and constructional apraxia subtests was recorded, whereas a worsening in short-term memory, working memory, attention and constructional apraxia subtests were shown after sham tDCS followed by cognitive computerized tasks cycle. In a larger sample, Boggio et al. (2012) assessed memory abilities before and after the application of five

consecutive sessions of active tDCS with two anodes over the temporal regions bilaterally in patients with AD. Visual recognition memory performance significantly improved after the treatment and the gain persisted for at least 4 weeks after the intervention, confirming the results of the previous studies showing improvement of recognition memory (Ferrucci et al., 2008; Boggio et al., 2009; Manenti et al., 2018).

Cotelli et al. (2014) investigated the effects of active tDCS with the anode over the left DLPFC combined with a memory training on face-name associations. The authors enrolled mild to moderate AD patients randomly assigned to one of three experimental groups, receiving respectively active or placebo tDCS during individualized computerized memory training or active tDCS during motor training. A general improvement in memory performance was observed after memory training (during active and during placebo tDCS) compared with motor training applied during active tDCS, suggesting a beneficial effect of individualized memory rehabilitation in AD patients. Regarding long-term effects the authors identified an improvement in the face-name association memory task 3 months after the intervention only in AD patients who received sham tDCS plus memory training compared with patients who received active tDCS plus motor training (both AD groups that received memory training maintained similar performances across all time points) failing to observe an additional effect of active tDCS. According to the authors, this lack of an additional effect might be related to some paradigm details. First, their study was the first study that applied daily tDCS combined with memory training, since in previous studies a single session or repeated sessions of tDCS alone were applied. This methodological change could be a reason for a positive effect in both AD samples that received memory training. Moreover, in their report they assessed associative memory (face and name) processing, an ability that involve two different kind of information to be retrieved: this particular kind of episodic memory could be more influenced by the memory training than by the active tDCS application.

Bystad et al. (2016) assessed the efficacy of 10 days of active tDCS with the anode over the left temporal cortex on verbal memory function in patients with AD. Adverse effects were not observed but the authors failed to observe a significant improvement induced by active tDCS as compared to sham stimulation in the neuropsychological assessment applied before and after the intervention.

Finally, in order to avoid the daily visit to the specialized centers and travel costs, Im et al. (2019) investigated changes in cognitive performances and regional cerebral metabolic rate (FDG-PET) after daily at-home active tDCS with the anode over left DLPFC for 6 months in

early AD patients. The first three tDCS sessions were performed at the hospital under the supervision of the research nurse. At the first session, the research nurse made sure a caregiver could independently apply tDCS at home. Compared to sham, active tDCS improved global cognition (MMSE) and language function (Boston Naming Test), without any change on episodic memory (Seoul verbal learning test and Rey Complex Figure Test). The lack of effects on delayed recall of episodic memory supports the findings of a previous study with aMCI (Manenti et al., 2018).
Moreover, regional cerebral metabolic rate in the left middle/inferior temporal gyrus was preserved in the active group, but decreased in the sham group.

In summary, these few studies on the effects of tDCS on episodic memory in AD patients have revealed mixed results (see Table 3 and Figure 2). Only two studies applied single sessions of tDCS (Boggio et al., 2009; Ferrucci et al., 2008), whereas most of the reported studies used multiple-sessions of tDCS to induce long-lasting effects (Andrade et al., 2016; Boggio et al., 2012; Bystad et al., 2016; Bystad et al., 2017; Im et al., 2019). Only two studies (one of them a single case study) investigated the effects of multiple-sessions of tDCS combined with a cognitive training (Cotelli et al., 2014; Penolazzi et al., 2015) suggesting that tDCS effects may not be always additive during a memory rehabilitation protocol. Only four studies assessed long-term effects of the intervention with inconclusive results (Boggio et al., 2012; Bystad et al., 2016; Cotelli et al., 2014; Penolazzi et al., 2015). At the neuronal level, a home based-tDCS has been shown to induce a stability of the regional cerebral metabolic rate in the left middle/inferior temporal gyrus (Im et al., 2019).
The studies that have applied tDCS in patients with AD have implemented different stimulation parameters, different treatment protocols and durations and, remarkably, different types of memory abilities assessment (within general batteries or as an in-depth evaluation). These differences make the comparison and the reaching of a conclusion difficult. Moreover, the interindividual variability between AD patients may make it even more difficult to compare the obtained results. Further work is needed to better understand the efficacy of tDCS in this population.

Insert Figure 2 about here
Insert Table 3 about here

7. Discussion

Most of the studies critically described in this review suggest that tDCS over the prefrontal or temporoparietal cortices can enhance episodic memory performance. The results of a recent meta-analysis suggested that tDCS holds great promise to ameliorate episodic memory decline in older individuals (Huo et al., 2019). However, the transfer to daily living activities of this intervention needs to be established. It appears that targeting individuals with healthy older adults or MCI might be a good strategy to prevent or delay the progression to AD. The paradigm shift of AD therapy from cure to prevention could be key to the success of disease modification (Cappa, 2018; Sindi et al., 2015).

There are important limitations that need to be acknowledged. Some tDCS studies had a small sample size and did not provide a sample size calculation, critical to gaining sufficient statistical power to detect a difference in the studies. In all the works with healthy older adults there is a lack of control site, important to determining that changes in memory performance are indeed specific to tDCS over a given brain area. In addition, most of studies did not use a tDCS modelling software (e.g. HD-target software, www.soterixmedical.com or SimNIBS, www.simnibs.org) to determine the optimal electrode configuration for the chosen brain target. Most of the studies with MCI lack information about in vivo biomarkers of degenerative conditions, such as advance neuroimaging (i.e. amyloid imaging), critical to determining if these patients are MCI due to AD (Albert, 2011). Moreover, only a few studies recorded surrogate outcomes of tDCS effects. The investigation of neural and biological changes induced by the intervention might clarify the bases for the behavioural changes and could guide the choice of the better parameters in order to induce the greatest effects.

There are important questions that need to be addressed in future works. The cortical target should be selected using structural magnetic resonance imaging (Sandrini et al., 2019), fMRI task-based (Woods et al., 2015) or rsfMRI (Wang et al., 2014). Target localization based on these MRI methods take into account individual structural and/or functional brain differences. Moreover, structural and functional imaging could be measured before stimulation to predict the responsiveness to tDCS interventions based on mapping of current flow, or individually selected brain targets based on resting-state or task activation (Boes et al., 2018; Gomes-Osman et al., 2018; Weigand et al., 2018).

Neuroimaging (MRI, MRS, EEG or magnetoencephalography, MEG) should be measured before and after multiple-sessions of tES to better understand the influence of stimulation on systems-level brain dynamics.

In addition, how variations in the presence of specific genetic polymorphisms (e.g. brain derived neurotrophic factor and apolipoprotein E ε4 allele) or brain structure (i.e. grey and white matter integrity) might influence the individual responsiveness remain open questions (Sandrini et al., 2018).

The optimal timing of stimulation to induce long-lasting effects (Manenti et al., 2016) deserves further investigation. Stimulation can have beneficial effects not only when applied during encoding/learning (Antonenko et al., 2018; Flöel et al., 2012; Medvedeva et al., 2019; Sandrini et al., 2016) but also during consolidation or reconsolidation (Manenti et al., 2018; Manenti et al., 2017; Sandrini et al., 2014; Sandrini et al., 2019). For example, a single session of tDCS during consolidation or reconsolidation induced long-lasting effects. A possible mechanism underlying this effect could be facilitation of consolidation (Au et al., 2017). Since the reactivation of encoded memories (or "replay") in subsequent waking state may be critical for memory consolidation (Karlsson and Frank, 2009; Sirota and Buzsaki, 2005), tDCS applied during awake periods, such as during consolidation (Rumpf et al., 2017; Sandrini et al., 2019; Tecchio et al., 2010) or reconsolidation (Javadi and Cheng, 2013; Manenti et al., 2018; Manenti et al., 2017; Sandrini et al., 2014), or so-tDCS applied during slow-wave sleep (Ladenbauer et al., 2016; Ladenbauer et al., 2017; Marshall et al., 2004; Westerberg et al., 2015) might boost neural reactivation and therefore enhance systems-level consolidation (Au et al., 2017; Manenti et al., 2018; Manenti et al., 2017). Regarding sleep, it might be worth exploring the possibility of applying tES during each patient's sleep cicle in an automated closed-loop manner (Ladenbauer et al., 2017). For example, it has been shown in young adults that closed-loop slow-oscillation transcranial alternating current stimulation (tACS), a technique that oscillates a sinusoidal current at a chosen frequency to interact with the endogenous oscillations (Battleday et al., 2014; Herrmann et al., 2013), improved episodic memory generalization by modulating slow oscillations (Ketz et al., 2018). Another exciting approach is offered by the combination of tACS with neuroimaging (e.g. EEG or fMRI, Hanslmayr et al., 2019; Thut et al., 2017; Violante et al., 2017), especially when applied taking into consideration EEG individual frequencies and phase coupling. For example, reduction in spontaneous gamma synchronization has been observed in AD patients (Gillespie et al., 2016; Stam et al., 2002) and driving hippocampal neurons at gamma frequency (40 Hz) reduced the levels of amyloid plaques in a mouse model of AD (Iaccarino et al., 2016). tACS at gamma frequency might prove to be useful for reducing the amyloid burden in AD.

Future studies should also investigate the effects of multiple sessions of tES with long-term follow-up. If a protocol includes multiple sessions of tES, the optimal spacing schedule of these sessions remains unknown. All of the studies reviewed here employ one daily session of stimulation, without any empirically derived model (Au et al., 2017). However, there is evidence that even shorter spacing protocols might have beneficial effects on cognitive functions (see for a review Goldsworthy et al., 2015).

In addition to conventional tDCS, the effects of more focal stimulation such high definition tDCS (HD-tDCS) (Edwards et al., 2013) have not been explored yet. The function of episodic memory network might be altered using network-targeted focal stimulation (e.g. HD-tDCS) as demonstrated with Transcranial Magnetic Stimulation (Hebscher and Voss, 2020). It has been shown that stimulation of the hippocampal network improves memory in ageing (Nilakantan et al., 2019), and critically demonstrated enhanced activity in the age-impaired hippocampal network.

There is also a strong rationale according to which tDCS and medications can work together for boosting therapeutic plasticity, eventually leading to a better clinical outcome (Perez et al., 2014; Sandrini et al., 2018). For example, tDCS applied with antidepressant drugs increased the efficacy of each single treatment in major depression (Brunoni et al., 2013) and tDCS associated with SRRI enhanced the process of memory formation in young and older adults (Prehn et al., 2017). The combination of tES with pharmacological interventions might be an important symptomatic therapy for individuals with aMCI, which represents the population of interest for the use of the so-called Disease-Modifying Therapies (Sandrini et al., 2018).

More open science efforts should be done to increase rigor and reliability in ageing populations. To our knowledge, only one Registered Report (Kiyonaga and Scimeca, 2019) conducted in young adults investigated the effect of tDCS over posterior parietal cortex in episodic memory reconsolidation (Crossman et al., 2019). Finally, there is also insufficient prepublication and sharing of materials (Buch et al., 2017; Lauer et al., 2015; Morey et al., 2016), particularly for negative results.

8. Conclusions

A growing body of work suggests the use of tES as a tool for neuromodulation of episodic memory in physiological and pathological ageing (Huo et al., 2019). However, many of the

reported effects still await replication and the clinical transferability in everyday life activities is almost nil.

More work is needed to better understand the brain mechanisms underlying the effects of multiple sessions of tES, the neural substrates of interindividual variability, and to optimize dosing and spacing schedules of stimulation.

Future studies should also investigate the optimal timing of stimulation and the combination with medications to induce long-lasting beneficial effects in pathological ageing.

Acknowledgments

We thanks Gergely Bartl, Cristina Alaimo, Elena Gobbi and Ilaria Pagnoni for their help in preparing of the manuscript

This work was supported by the Italian Ministry of Health (Ricerca Corrente).

Figure captions

Figure 1. Schematic illustration of the memory formation and modification with stimulation timing.

For a limited time after encoding, memories undergo an initial unstable (fragile) phase, before being stabilized through the consolidation process. However, consolidated memories may return to an unstable (fragile) phase when they are retrieved or reactivated by a reminder, thus requiring a restabilization process that is known as reconsolidation. During this time-limited reconsolidation window, consolidated memories can be degraded, strengthened, or updated by the inclusion of new information. Arrows show when tES was applied. Modified from Sandrini et al. (2015) with permission from Elsevier.

Figure 2. Studies that tested cognitive functions, including episodic memory, before and after single/multiple tDCS session(s) with or without training are reported. Some of them also included a follow up (T3).

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Table 1. tDCS or so–tDCS in healthy older adults

Study ID Older Adults		Participants enrolled and mean age	Number of stimulation sessions	Design	Blinding	Intensity	Electrode surface	Duration	Electrodes location: 10/20 EEG
1	Antonenko et al., 2018	N=40 Mean age: 70	3	Parallel	Single	1mA	Anode: 7x5 cm^2 Cathode 10x10cm^2	20 mins	Anode: T6 Cathode: Fp2
2	Antonenko et al., 2019	N=34 Mean age: 63.1	1	Crossover	Single	1mA	Anode: 7x5cm^2 Cathode 10 x 10cm^2	20 mins	Anode: CP5 Cathode: the right supraorbital area (centered over the right anterior frontal cortex, or AF4)
3	Brambilla et al., 2015	N=32 Mean age: 67.9	1	Crossover	Single	1.5mA	Anode: 7×5cm^2 Cathode: 7×5cm^2	6 mins	Anode: right or left DLPFC and PPC Cathode: the contralateral supraorbital area
4	Eggert et al., 2013 so-tDCS	N=26 Mean age: 69.1	1	Crossover	Double	0.26mA	Diameter =10mm	26 mins (5m16s x 5 times)	Anode: bilateral F3 and F4 Cathode: bilateral mastoids

5	Flöel et al., 2012	N=20 Mean age: 62.1	1	Crossover	Double	1mA	Anode: 5x7cm² Cathode: 10x10cm²	20 mins	Anode: between P4 and T6 Cathode: the contralateral supraorbital region
6	Külzow et al., 2018	N=32 Mean age: 68	3	Crossover	Single	1mA	Anode: 7x5 cm² Cathode: 10x10cm²	20 mins	Anode: T6 Cathode: the contralateral supraorbital region
7	Ladenbauer et al., 2016 so-tDCS	N=18 Mean age: 65	1	Crossover	Single	0.26mA	diameter=8mm	5 x 5mins	Anode: bilateral F3 and F4 Cathode: bilateral mastoids
8	Leach et al., 2018	N=48 Mean age: 65.63	1	Crossover	Double	1.5mA	Anode: 3.3x3.3 cm² Cathode: 3.3x3.3 cm²	25 mins	Anode: F3 Cathode: the contralateral upper arm
9	Manenti et al., 2013	N=64 Mean age: 67.91	1	Crossover	Single	1.5mA	Anode: 7×5cm² Cathode: 7x5cm²	6 mins	Anode: right or left DLPFC and PPC Cathode: the contralateral supraorbital area
10	Manenti et al., 2017	N=22 Mean age: 74.5	1	Parallel	Double	1.5mA	Anode: 7×5cm² Cathode: 7x5cm²	15 mins	Anode: F3 Cathode: Fp2

11	Medvedeva et al., 2019	N=26 Mean age: 73	1	Parallel	Single	2mA	Anode: 5x7cm² Cathode: 5x7cm²	9 mins	Anode: F7 Cathode: contralateral deltoid area
12	Paßmann et al., 2016 so-tDCS	N=21 Mean age: 65	1	Crossover	Single	0.26mA	diameter=8mm	5 x 5 mins	Anode: bilateral F3 and F4 Cathode: bilateral F3 and F4
13	Sandrini et al., 2014	N=36 Mean age: 67.17	1	Parallel	Single	1.5mA	Anode: 7×5cm² Cathode: 7×5cm²	15 mins	Anode: F3 Cathode: the right supraorbital area
14	Sandrini et al., 2016	N=28 Mean age: 68.9	1	Parallel	Single	1.5mA	Anode: 7×5cm² Cathode: 7×5cm²	15 mins	Anode: F3 Cathode: the right supraorbital area
15	Sandrini et al., 2019	N=28 Mean age: 68.6	1	Parallel	Double	1.5mA	Anode: 7×5cm² Cathode: 7×5cm²	15 mins	Anode: F3 Cathode: Fp2 the right supraorbital area
16	Westerberg et al., 2015 so-tDCS	N=19 Mean age: 73.4	5	Crossover	Double	0.26mA	diameter=8mm	5 x5 mins	Anode: bilateral F7 and F8 Cathode: ipsilateral mastoids

Table 2. tDCS or so-tDCS in patients with Mild Cognitive Impairment (MCI)

Study ID Mild Cognitive Impairment (MCI)		Participants enrolled and mean age	Number of timulation sessions	Design	Blinding	Intensity	Electrode surface	Duration	Electrodes location 10/20 EEG
1	Das et al., 2019	N=22 Mean age: 62.9	8	Parallel	Double	2mA	Anode: 3x5 cm^2 Cathode: 3x5	20 mins	Anode: left IFG Cathode: the right shoulder
2	Fileccia et al., 2019	N=34 Mean age: 71.6	20	Parallel	Double	2mA	Anode: 7x5 cm^2 Cathode: 7x6	20 mins	Anode: F3 DLPFC Cathode: the right deltoid muscle
3	Gomes et al., 2019	N=58 Mean age: Active: 73 Sham: 71.6	10	Crossover	Double	2mA	Anode: 5x5 cm^2 Cathode 5x5 cm^2	30 mins	Anode: F3 Cathode: the right supraorbital area, Fp2
4	Ladenbauer et al., 2017 so-tDCS	N=220. Mean age: 71.2	1	Crossover	Single	0.26mA	diameter=8mm	25 mins (5 x 5mins)	Anode: bilateral F3 and F4 Cathode: bilateral mastoids
5	Manenti et al., 2018	N=18 Mean age: 75.3	1	Parallel	Double	1.5mA	Anode: 7×5cm^2 Cathode: 7x5cm^2	15 mins	Anode: F3 Cathode: Fp2
6	Murugaraja et al., 2017	N=11 Mean age: 59.6	5	Open label	None	2mA	Anode: 7×5cm^2 Cathode: 7×5cm^2	20 mins	Anode: Between F3 and FP1 Cathode: the right supra orbital region

7	Yun et al., 2016	N=16 Mean age: 74.7	9	Parallel	Double	2mA	Anode: 5x5 cm^2 Cathode 5x5 cm^2	30 mins	Anode: F3 Cathode: F4
8	Lu et al., 2019	N=201 Aged from 60 to 90 years	12	Parallel	Double	2mA	Anode: 5x7cm^2 Cathode: 5x7cm^2	20 mins	Anode: T3 Cathode: contralateral upper limb

Table 3. tDCS in patients with Alzheimer's disease (AD)

Study ID Alzheimer's Disease (AD)		Participants enrolled and mean age	Number of stimulation sessions	Design	Blinding	Intensity	Electrode surface	Duration	Electrodes location 10/20 EEG
1	Andrade et al., 2016	N=1 Age: 73	10	Case study	Open label	2mA	Anode: 5x7 cm^2 Cathode 5x7 cm^2	30 mins	Anode: F3 Cathode: the right supra orbital region
2	Boggio et al., 2009	N=10 Mean age: 79.1	1	Crossover	single	2mA	Anode: 7×5cm^2 Cathode: 7×5cm^2	30 mins	Anode: F3 or T7 Cathode: the right supra orbital region
3	Boggio et al., 2012	N=15 Mean age: Italian P.: 77.5 Brazilian P.: 80.6	5	Crossover	double	2mA	Anode: 7×5cm^2 Cathode: 7×5cm^2	30 mins	Anode: bilateral F3 and F4 Cathode: the right deltoid muscle
4	Bystad et al., 2016a	N=25 Mean age: Active: 70.2 Sham: 75.0 Control: 68.8	6	Parallel	double	2mA	Anode: 7×5cm^2 Cathode: 7×5cm^2	30 mins	Anode: T3 Cathode: FP2

5	Bystad et al., 2016b	N=1 Age: 59	12	Case study	No sham	2mA	Not reported	30 mins	Anode: T3 Cathode: FP2
6	Bystad et al., 2017	N=1 Age: 60	Daily for six months	Case study	No sham	2A	Not reported	30 mins	Anode: T3 Cathode: FP2
7	Cotelli et al., 2014	N=36 Mean age: Active: 73 Sham: 71.6	10	Parallel	double	2mA	Anode: 5x5 cm^2 Cathode 6x10 cm^2	25 mins	Anode: F3 Cathode: the right supra orbital region
8	Ferrucci et al., 2008	N=10 Mean age: 75.2	1	Crossover	Double	1.5mA	Anode: 5x5cm^2 Cathode: not reported	15 mins	Anode: Bilateral P3-T5, P6-T4 Cathode: the right deltoid muscle
9	Im et al., 2019	N=18 Mean age: Active: 71.9 Sham: 74.9	Daily for 6 months	Crossover	Double	2mA	Anode: diameter=6cm Cathode: diameter=6cm	30 mins	Anode: F3 Cathode: F4

10	Penolazzi et al. 2015	N=1 Age: 60	10	Case study, Crossover	Single	2mA	Anode: 5x7 cm^2 Cathode 10x10 cm^2	20 mins	Anode: F3 Cathode: Right supraorbital area

Figure 1

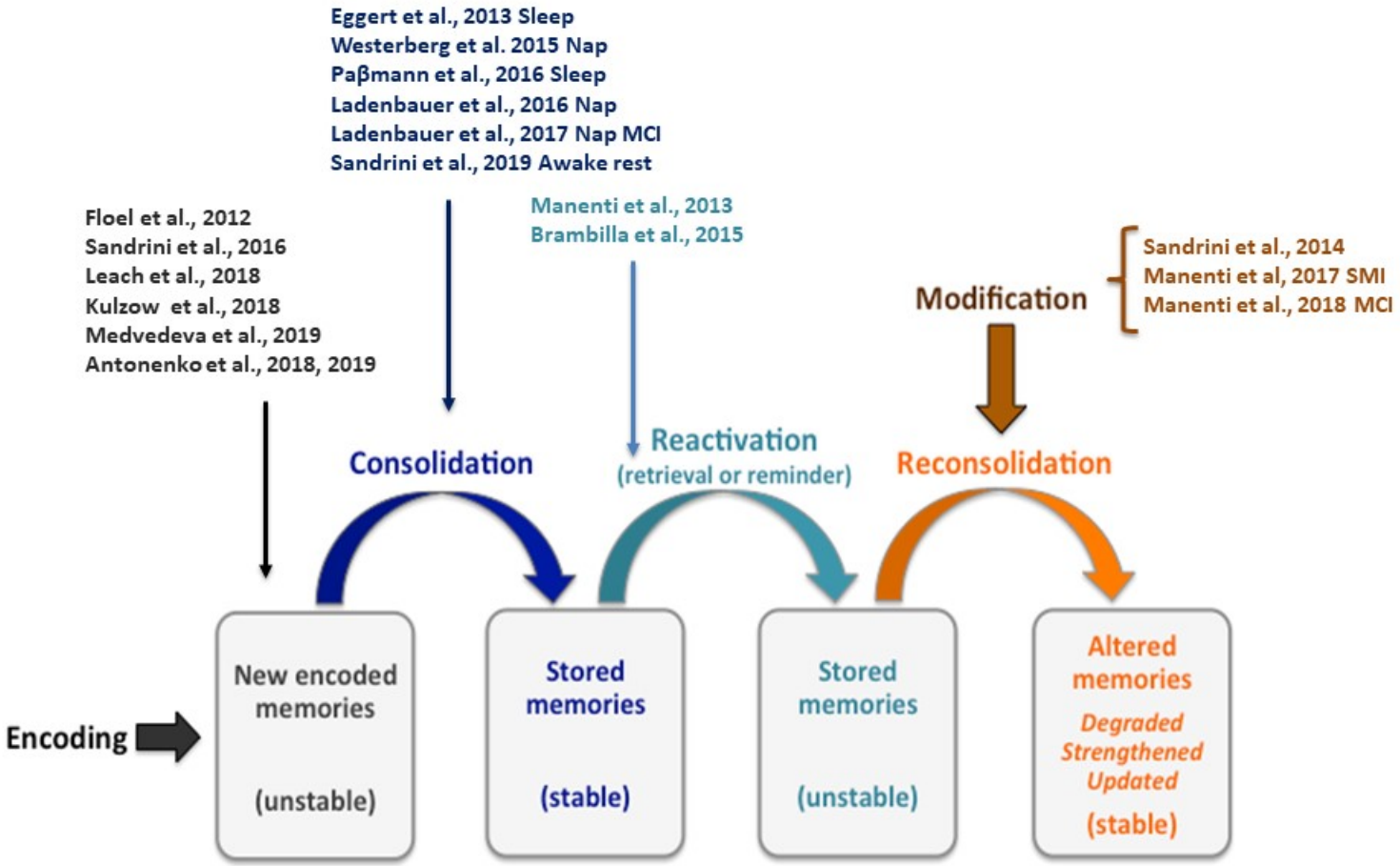
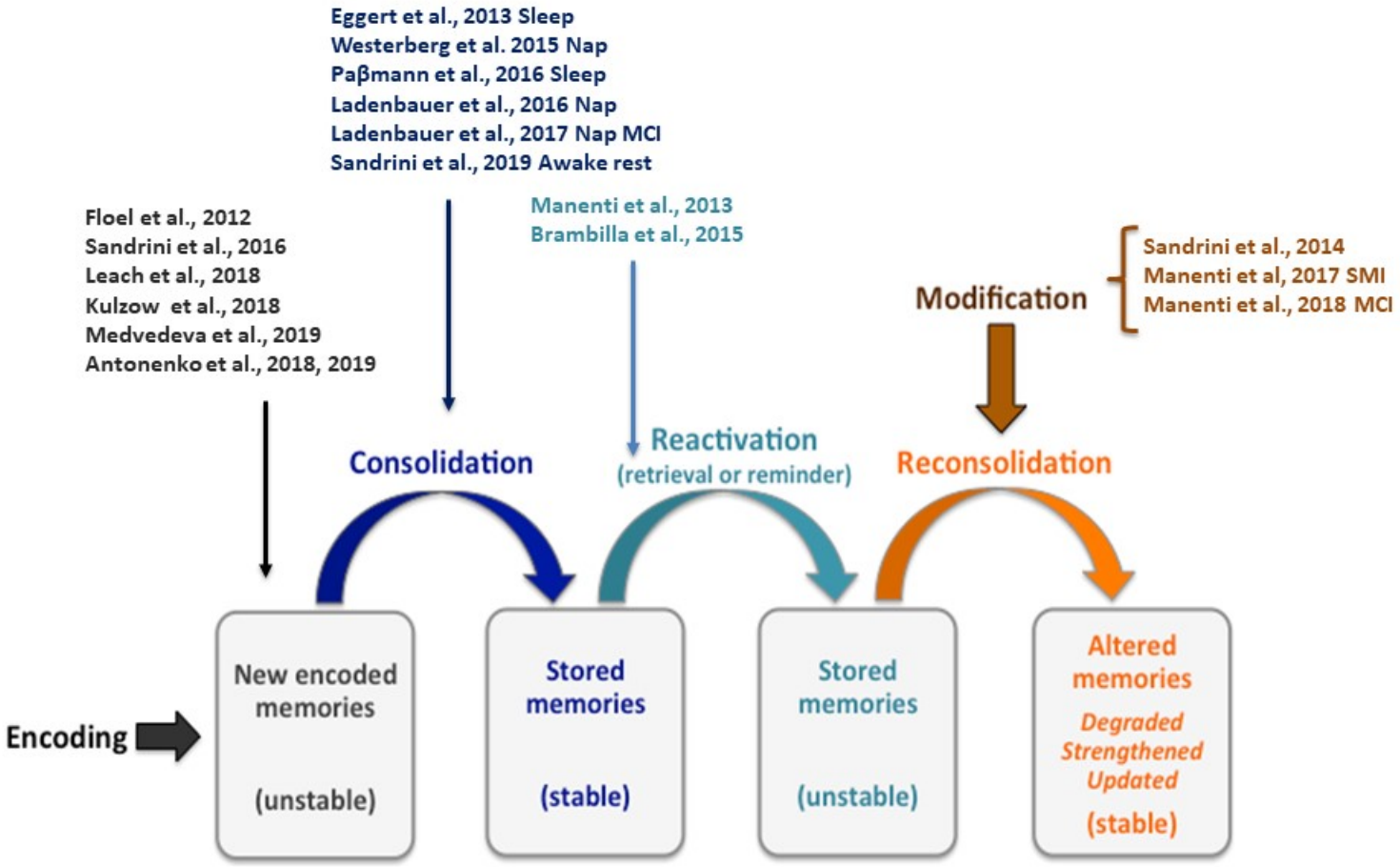

Eggert et al., 2013 Sleep
Westerberg et al. 2015 Nap
Paβmann et al., 2016 Sleep
Ladenbauer et al., 2016 Nap
Ladenbauer et al., 2017 Nap MCI
Sandrini et al., 2019 Awake rest
Floel et al., 2012
Sandrini et al., 2016
Leach et al., 2018
Kulzow et al., 2018
Medvedeva et al., 2019
Antonenko et al., 2018, 2019
Manenti et al., 2013
Brambilla et al., 2015
Modification
Sandrini et al., 2014
Manenti et al, 2017 SMI
Manenti et al., 2018 MCI
Consolidation
Reactivation
(retrieval or reminder)
Reconsolidation
Encoding
New encoded memories
(unstable)
Stored memories
(stable)
Stored memories
(unstable)
Altered memories
Degraded
Strengthened
Updated
(stable)

Figure 2


Eggert et al., 2013 Sleep
Westerberg et al. 2015 Nap
Paβmann et al., 2016 Sleep
Ladenbauer et al., 2016 Nap
Ladenbauer et al., 2017 Nap MCI
Sandrini et al., 2019 Awake rest
Floel et al., 2012
Sandrini et al., 2016
Leach et al., 2018
Kulzow et al., 2018
Medvedeva et al., 2019
Antonenko et al., 2018, 2019
Manenti et al., 2013
Brambilla et al., 2015
Modification
Sandrini et al., 2014
Manenti et al, 2017 SMI
Manenti et al., 2018 MCI
Consolidation
Reactivation
(retrieval or reminder)
Reconsolidation
Encoding
New encoded memories
(unstable)
Stored memories
(stable)
Stored memories
(unstable)
Altered memories
Degraded
Strengthened
Updated
(stable)